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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YAKOVLEVA, GALINA M	
ART UNIT	**PAPER NUMBER**
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,039	SONGE, PAL	
	Examiner	Art Unit	
	GALINA YAKOVLEVA	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-39* is/are rejected.

7)☒ Claim(s) *23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner charged with the present case has changed. See contact information below. Responsive to communications entered 07/07/2010.

Status of Claims

The set of claims, as amended on 07/07/2010, contains two claims numbered 34. Misnumbered claims 34-38 have been renumbered 35-39. The amended set of Claims 23-39 is required.

Claims 23-39 are pending. Claims 1-22 are cancelled. Claims 23-39 are examined.

Priority

The instant application, 10/599,039, Publication No. US 2007/0299249, is the 35 U.S.C 371 filing of PCT/GB05/00991, filed on 03/17/2005, which claims foreign priority to GB 0406015.8, filed 03/17/2004, and benefit of U.S. Provisional Application 60/592,034, filed on 07/29/2004. It is noted that foreign priority to GB 0406015.8 is claimed in the Declaration. However, in the Application Data Sheet 37 CFR 1.76, GB 0406015.8 is identified as a prior foreign application for which priority is not claimed. Please clarify.

Information Disclosure Statement

No information disclosure statement is submitted for the instant application. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states,

"the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objection

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

The set of claims, as amended on 07/07/2010, contains two claims numbered 34. Misnumbered claims 34-38 have been renumbered 35-39.

Claim 23 is objected to because of the following informalities. In recitation "contacting the tagged protein with a conjugate of a chelating agent and *a* polymer particle," instead of an article "a" shall be used an article "the." Emphasis added. Appropriate correction is required.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 is intended to cover a plurality of particles of Claim 38. There is insufficient antecedent basis for this recitation in Claim 38, which is drawn to a protein covalently bound to a magnetic polymer particle.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Nelson** *et al.*, U.S. Patent No. 5,962,641, issued on 10/05/1999 (cited in the specification), in view of **Chaga** *et al.*, (1999). "Natural poly-histidine affinity tag for purification of recombinant proteins on cobalt(II)-carboxymethylaspartate crosslinked agarose". *J. Chromatogr. A* **864** (2), pages 247-256; and **Minh**, U.S. Patent No. 6,441,146, issued on 08/27/2002 (cited in the specification), and further in view of

Ugelstad *et al.*, U.S. Patent No. 4,654, 267, issued on 03/31/1987 (cited in the specification).

Claims 23-35, as recited in independent Claim 23, are drawn to a process for covalently binding a tagged protein to a polymer particle, the process comprises contacting the tagged protein with a conjugate of a chelating agent and a polymer particle to form a protein-polymer particle-chelating agent metal ion complex, and contacting the complex with a carbodiimide to form a covalently bound protein; wherein the tag comprises at least two histidine residues and at least two lysine residues; the chelating agent is tridentate, tetradentate, or pentadentate, comprises at least two carboxyl groups and coordinated by a metal ion. Claim 30 requires the polymer particle to be magnetic. Claim 36 is drawn to a covalently bound protein obtained by the process of claim 23. Claim 37 is drawn to a protein bound to a polymer particle having the specified structure. Claim 38 is drawn to a protein covalently bound to a magnetic polymer particle. Claim 39 is drawn to a plurality of particles.

Nelson *et al.*, throughout the patent and, for example, in Abstract, Col. 4, lines 19-22 and 28-29, teach purification of poly-amino acid-tagged recombinant proteins, for example, having a polyhistidine tail or "tag," using a carboxymethylated aspartate ligand complexed with a third-block transition metal having an oxidation state of 2^+ and a coordination number of 6, such as Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, or Zn^{2+} in an octahedral geometry. At Col. 2, lines 17-28, Claims 1 and 2, Nelson *et al.* teach preparation of caboxymethylated aspartate ligand attached to a polymer matrix, for example, agarose, wherein the ligand meets the structural limitations recited in Claim 37 of the instant

application. At Col. 4, lines 29-32, Nelson *et al*. teach use of other polymer matrices, e.g., polystyrene (as in microtiter plates), nylon (as in nylon filters), SEPHAROSE (Pharmacial, Uppeala, Sweden) or the like. At Col. 4, lines 54-60, Nelson *et al*. teach that Co^{2+} can be preferably used as the transition metal with CM-Asp because the Co^{2+}-CM-Asp can be less sensitive to reducing agents, such as β-mercaptoethanol, and metal ion leakage has been shown to remain low, even negligible, in the presence of up to 30 mM β-mercaptoethanol.

Nelson *et al*. do not teach a tag comprises at least two histidine residues and at least two lysine residues.

Cĥaga *et al*., throughout the publication and, for example, in Abstract, Materials and Methods, Fig. 1, teach the use of a natural 19-amino acid poly-histidine affinity tag (HAT) from lactate dehydrogenase, which HAT contains 6 histidine residues and 3 lysine residues, for preparing HAT-tagged proteins, such as recombinant chloramphenicol acetyltransferase (CAT), dihydrofolate reductase (DHFR) and green fluorescent protein – UV-enhanced variant (GFPuv) tagged with the HAT sequence. At page 248, right column, Cĥaga *et al*. teach synthesis of carboxymethylaspartate (CM-Asp) crosslinked agarose (Superflow). At page 249, right column, Cĥaga *et al*. teach the use of Co^{2+} ions immobilized on CM-Asp Superflow for rapid one-step purification of CAT, DHFR and GFPuv tagged with the HAT sequence in one chromatographic step. At page 254, right column, Cĥaga *et al*. teach that the tag appears to be readily exposed in all three of the example proteins. At page 255, left column, Cĥaga *et al*. teach that the affinity of the HAT-tagged proteins for Co^{2+} ions immobilized on CM-Asp

is high, and the conditions for purification are very mild (neutral pH, low salt) and good recoveries were observed with all three example proteins.

Neither Nelson *et al*. nor Cĥaga *et al*. teach contacting a protein-polymer particle-chelating agent metal ion complex with a carbodiimide to form a covalently bound protein.

Minh, throughout the patent and, for example, in Abstract, Example 6, Claim 1, teaches purification of histidine containing biomolecules such as proteins or peptides, for example, having a polyhistidine tag, using pentadentate chelator (PDC) porous resins capable of forming the octahedral complexes with several polyvalent metal ions including Co^{2+}, Ni^{2+}, Cu^{2+}, or Zn^{2+} with five coordination sites occupied by the chelator. In Claims 8-11, Example 12, Minh teaches the use of Cu-PDC porous resins for covalent immobilization of proteins, using a soluble carbodiimide, and removal of the divalent metal Cu^{2+} from the protein-PDC resin complex with ethylenediaminotetraacetic acid (EDTA) in order to obtain the protein covalently attached to the PDC resin.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have contacted a protein-polymer particle-chelating agent metal ion complex, taught by Nelson *et al*. and Cĥaga *et al.,* with a carbodiimide to form a covalently bound protein, as taught by Minh.

One of ordinary skill in the art would have been motivated to have contacted a protein-polymer particle-chelating agent metal ion complex, taught by Nelson *et al*. and Cĥaga *et al.,* with a carbodiimide to form a covalently bound protein, as taught by Minh,

because it would be desirable to provide specific capturing of a tagged protein through covalent immobilization on a solid support.

One of ordinary skill in the art would have had a reasonable expectation of success in contacting a protein-polymer particle-chelating agent metal ion complex, taught by Nelson *et al*. and Cĥaga *et al.,* with a carbodiimide to form a covalently bound protein, as taught by Minh, because the HAT-tag, taught by Cĥaga *et al.,* contains 3 lysine residues, which, upon treatment with the carbodiimide, are capable of covalently binding to the carboxyl groups of CM-Asp chelating agent through amide linkages with their side chain amino groups.

Nelson *et al*. as well as Cĥaga *et al*. or Minh do not teach their chelating ligand attached to a magnetic polymer particle.

Ugelstad *et al*. teach magnetic polymer particles (made of Fe^{2+}, Mn^{2+}, Co^{2+} and Ni^{2+}) meeting the limitations of Claims 30, 32, 38 and 39, and method of their preparation, wherein said ions are oxidized to higher oxidation state in a polymer (e.g. styrene mixture) matrix, to be deposited in non-soluble form therein rendering the matrix magnetic. In Column 2, lines 9-11, Ugelstad *et al*. teach that the process used is suitable for preparing particles in the range of 0.5-20 μm, but it may also be used for the preparation particles smaller than 0.5 μm. In Column 2, lines 9-11, Claim 9, Ugelstad *et al*. teach the monodisperse particles of desired size, compact as well as porous. In column 1, Ugelstad *et al*. teach that such particles may be used to replace a method of separation of particles by means of centrifugation.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to start with the chelating ligand of Nelson *et al*. and substitute its R3 (polymer matrix, see column 2) with magnetic polymer matrix (particles) of Ugelstad *et al*.

One of ordinary skill in the art would have been motivated to substitute the supporting polymer matrix of Nelson *et al*. with magnetic polymer matrix (particles) of Ugelstad *et al*. because it would be desirable to obtain a product, which can be easily recovered from a solution by a magnet such that costly and time consuming centrifugation step will be eliminated.

One of ordinary skill in the art would have had a reasonable expectation of success in using such magnetic polymer matrix/aspartate chelating ligand conjugates because magnetic polymer matrix conjugates are well-known in the art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-17, 19-23 and 27 of copending Application No. 12/643,617 (the '**617** application), PGPUB 2010/0222508, which is a continuation of Application No. 10/562,694, now abandoned, in view of **Chaga** *et al*., (1999). "Natural poly-histidine affinity tag for purification of recombinant proteins on cobalt(II)-carboxymethylaspartate crosslinked agarose". *J. Chromatogr. A* **864** (2), pages 247-256; and **Minh**, U.S. Patent No. 6,441,146, issued on 08/27/2002 (cited in the specification).

The '**617** application claims a conjugate comprising a magnetic polymer particle (MPP) bound to a carboxymethylated aspartate chelating ligand (Claims 1-17); a compound (a CM-Asp ligand) (Claims 20-22); a process for the preparation of the conjugate (Claim 19) or compound (Claim 23); and a method of purifying a histidine-tagged recombinant protein or peptide, using the conjugate of Claim 2.

Cĥaga *et al*., throughout the publication and, for example, in Abstract, Materials and Methods, Fig. 1, teach the use of a natural 19-amino acid poly-histidine affinity tag (HAT) from lactate dehydrogenase, which HAT contains 6 histidine residues and 3 lysine residues, for preparing HAT-tagged proteins, such as recombinant chloramphenicol acetyltransferase (CAT), dihydrofolate reductase (DHFR) and green fluorescent protein – UV-enhanced variant (GFPuv) tagged with the HAT sequence. At page 248, right column, Cĥaga *et al*. teach synthesis of carboxymethylaspartate (CM-Asp) crosslinked agarose (Superflow). At page 249, right column, Cĥaga *et al*. teach the use of Co^{2+} ions immobilized on CM-Asp Superflow for rapid one-step purification of CAT, DHFR and GFPuv tagged with the HAT sequence in one chromatographic step. At page 254, right column, Cĥaga *et al*. teach that the tag appears to be readily exposed in all three of the example proteins. At page 255, left column, Cĥaga *et al*. teach that the affinity of the HAT-tagged proteins for Co^{2+} ions immobilized on CM-Asp is high, and the conditions for purification are very mild (neutral pH, low salt) and good recoveries were observed with all three example proteins.

Minh, throughout the patent and, for example, in Abstract, Example 6, Claim 1, teaches purification of histidine containing biomolecules such as proteins or peptides, for example, having a polyhistidine tag, using pentadentate chelator (PDC) porous resins capable of forming the octahedral complexes with several polyvalent metal ions including Co^{2+}, Ni^{2+}, Cu^{2+}, or Zn^{2+} with five coordination sites occupied by the chelator. In Claims 8-11, Example 12, Minh teaches the use of Cu-PDC porous resins for covalent immobilization of proteins, using a soluble carbodiimide, and removal of the

divalent metal Cu^{2+} from the protein-PDC resin complex with ethylenediaminotetraacetic acid (EDTA) in order to obtain the protein covalently attached to the PDC resin.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used a conjugate comprising a magnetic polymer particle (MPP) bound to a carboxymethylated aspartate chelating ligand, claimed in the '**617** application, for covalently binding a tagged protein, taught by Chaga *et al.,* using a carbodiimide, as taught by Minh.

One of ordinary skill in the art would have been motivated to have used a conjugate comprising a magnetic polymer particle (MPP) bound to a carboxymethylated aspartate chelating ligand, as claimed in the '**617** application, for covalently binding a tagged protein, taught by Chaga *et al.,* using a carbodiimide, as taught by Minh, because it would be desirable to obtain a product, which can be easily recovered from a solution by a magnet such that costly and time consuming centrifugation step will be eliminated.

One of ordinary skill in the art would have had a reasonable expectation of success in using such magnetic polymer matrix/aspartate chelating ligand conjugates because magnetic polymer matrix conjugates are well-known in the art.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Claims 23-39 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GALINA YAKOVLEVA whose telephone number is (571)270-3282. The examiner can normally be reached on Monday-Friday 8:00 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571)272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G. Y./
Examiner, Art Unit 1641

/Mark L. Shibuya/
Supervisory Patent Examiner, Art Unit 1641